*167409 PAIRED BOX GENE 2; PAX2

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Database Links

Gene Map Locus: 10q24.3-q25.1

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TEXT

Pilz et al. (1993) used mouse cDNA probes for Pax2 to map the human homolog of the gene in somatic cell hybrids. PAX2 showed complete concordance with human chromosome 10. Further analysis with hybrids made from a human cell line with a reciprocal translocation showed that PAX2 maps to 10q11.2-qter. The homologous gene maps to mouse chromosome 19. By analysis of somatic cell hybrids and by fluorescence in situ hybridization (FISH), Stapleton et al. (1993) assigned PAX2 to 10q25.

Narahara et al. (1997) described a 5-year-old boy with a de novo t(10;13) translocation and optic nerve coloboma-renal syndrome (120330). By FISH using a YAC clone containing the PAX2 gene and YAC clones adjoining FRA10B, a fragile site at 10q25.2, Narahara et al. (1997) demonstrated that the 10q break had occurred just within the PAX2 gene and was proximal to FRA10B. They refined the regional mapping of the PAX2 gene to the junction of bands 10q24.3 and 10q25.1.

Sanyanusin et al. (1996) obtained the complete genomic structure of the human PAX2 gene. They described 5 genomic lambda clones containing human PAX2 gene sequences, 4 of which had previously been reported by them (Sanyanusin et al., 1995). The fifth clone, which included exons 7 and 8, was obtained by Sanyanusin et al. (1996) from a subgenomic lambda cDNA library of size-fractionated EcoRI fragments ranging in size from 6 to 8 kb. Sequencing and restriction mapping of these clones showed that the human PAX2 gene is composed of 12 exons spanning approximately 70 kb. They also found 2 alternatively spliced exons corresponding to exon 10 (Ward et al., 1994) and a 69-bp inserted sequence that they designated as exon 6. The 69-bp insert is homologous to a 69-bp insert reported in the murine Pax2 gene by Dressler et al. (1990). Sanyanusin et al. (1996) identified a (CA)n dinucleotide repeat polymorphism in PAX2 which they mapped immediately upstream of exon 9.

The PAX2 gene is expressed in primitive cells of the kidney, ureter, eye, ear, and central nervous system. Based on the known expression pattern of PAX2, Sanyanusin et al. (1995) predicted that the phenotype caused by mutations of PAX2 would probably consist of autosomal dominant eye malformations, sensorineural hearing loss, and renal hypoplasia. Pursuing this suspicion, they found deletion of a single nucleotide in exon 5 of the PAX2 gene (167409.0001) in a father and 3 of his 5 sons who had optic nerve colobomas, renal hypoplasia, mild proteinuria, and vesicoureteral reflux. The nucleotide deletion caused a frameshift in the conserved octapeptide sequence. The phenotype was similar to that of Krd mutant mice which lack a portion of chromosome 19 that is homologous to human 10q24 and includes the Pax2 gene. These mice have reduced thickness of the renal cortex, a reduced number of glomeruli at birth, and reduced amplitudes on electroretinogram. In the Krd mouse, the deletion of chromosome 19 was transgene-induced (Keller et al., 1994). Coloboma of the optic nerve with renal disease (120330) is a recognized syndrome. Renal dysplasia and retinal aplasia are combined in the Loken-Senior syndrome (266900). Ocular abnormalities occur also with familial juvenile nephronophthisis (256100), but that disorder maps to chromosome 2.

In the developing kidney, induction of nephrogenesis by the ureter is accompanied by an increase in expression levels of the PAX2 gene. This is followed by an increase in expression of WT1 (607102), the Wilms tumor suppressor gene, as mesenchymal cells condense and differentiate. In studies in cultured cells, Dehbi et al. (1996) demonstrated that PAX2 isoforms are capable of transactivating the WT1 promoter. Deletion mutagenesis of the WT1 promoter identified an element responsible for mediating PAX2 responsiveness, locating it between nucleotides -33 and -71 relative to the first WT1 transcription start site. They demonstrated that PAX2 can stimulate expression of the endogenous WT1 gene. These results suggested to Dehbi et al. (1996) that a role for PAX2 during mesenchyme-to-epithelium transition in renal development is to induce WT1 expression.

Using in situ hybridization on paraffin-embedded human embryo sections at 5 different stages (days 32 to 60), Tellier et al. (2000) showed that PAX2 is expressed (1) in the optic vesicle and later in the retina, (2) in the otic vesicle and later in the semicircular canals of the inner ear, and (3) in mesonephros, metanephros, adrenals, spinal cord, and hindbrain. Based on this expression pattern, they screened the entire coding region of the PAX2 gene for mutations in 34 patients fulfilling the diagnostic criteria for CHARGE association (214800) using 2 polymorphisms to look for deletions and SSCP of the 12 exons to look for nucleotide variations. No disease-causing mutations were identified, suggesting that mutation of the PAX2 gene is not a common cause of CHARGE association. The authors suggested that the expression pattern of PAX2 is consistent with the possibility that unidentified PAX2 downstream targets and effectors could be candidate genes for CHARGE. Tellier et al. (2000) screened 2 patients with the CHARGE/DiGeorge association, 21 cases of isolated renal hypoplasia (191830), and 4 cases of the renal-coloboma syndrome (RCS) (Tellier et al., 1998). They observed heterozygous PAX2 gene mutations in the following situations: (1) a dinucleotide insertion (619insGG; 167409.0009) in a sporadic case of RCS; (2) a 6-bp deletion in an isolated case of renal hypoplasia; (3) a single nucleotide insertion (619insG; 167409.0002) in 3 renal hypoplasia cases, either isolated or associated with microphthalmia and retinal degeneration. The recurrent 619insG mutation had previously been reported in 1 sporadic and 2 familial cases of RCS; the same mutation in Pax2 is responsible for the 1Neu mutant, a mouse model for human RCS. No PAX2 mutation was found in CHARGE or in CHARGE/DiGeorge patients. The study confirmed the critical role of PAX2 in human renal and ocular development and probably otic development. It also demonstrated that PAX2 mutations can be responsible for renal hypoplasia, either isolated or associated with various ophthalmologic manifestations ranging from retinal coloboma to microphthalmia.

Schimmenti et al. (1999) described a mildly affected Caucasian mother and daughter and a severely affected African-American girl, all of whom had PAX2 homoguanine tract (7G) missense mutations.

The mother and daughter had optic nerve colobomas and the daughter had vesicoureteral reflux. The severely affected girl developed renal failure and had bilateral colobomatous eye defects. Additionally, this girl developed hydrocephalus associated with platybasia and a Chiari-1 malformation. The severely affected girl showed a previously described mutation (Sanyanusin et al., 1995; Schimmenti et al., 1995), the insertion of a guanine into the homoguanine tract of 7 residues between positions 613 and 619 (167409.0002). The mother and daughter demonstrated heterozygosity for a previously undescribed mutation: a contraction of the homonucleotide tract from 7 guanines to 6 guanines in exon 2 of PAX2 (167409.0008), leading to a premature stop codon 2 amino acids downstream. This mutation was not present in unaffected relatives. Thus, the known phenotype associated with mutations in PAX2 was expanded to include brain malformations. The homoguanine tract in PAX2 is a hotspot for spontaneous expansion or contraction mutations and demonstrates the importance of homonucleotide tract mutations in human malformation syndromes.

In a study of 9 patients with renal-coloboma syndrome, Amiel et al. (2000) screened the entire coding sequence of the PAX2 gene and found 5 heterozygous mutations. The 619insG mutation was detected in 3 unrelated cases and the dinucleotide insertion GG at the same position was found in an isolated case, further confirming the stretch of 7 guanines as a mutation hotspot. The 619insG mutation was detected in 2 isolated cases and in a family with 3 affected sibs whose unaffected parents did not carry the mutation, suggesting germline mosaicism (false paternity excluded).

To gain insight into the cause of renal abnormalities in patients with PAX2 mutations, Porteous et al. (2000) analyzed kidney anomalies in patients with RCS, including a large Brazilian kindred in which they had identified a novel mutation. In a total of 29 patients, renal hypoplasia was the most common congenital renal abnormality. To determine the direct effects of PAX2 mutations on kidney development, fetal kidneys of mice carrying a Pax2(1Neu) mutation were examined. At embryonic day 15 (E15), heterozygous mutant kidneys were approximately 60% the size of those of wildtype littermates, and the number of nephrons was strikingly reduced. Heterozygous mutant mice showed increased apoptotic cell death during fetal kidney development, but the increased apoptosis was not associated with random stochastic inactivation of Pax2 expression in mutant kidneys; Pax2 was shown to be biallelically expressed during kidney development. The findings supported the conclusion that heterozygous mutations of the PAX2 gene are associated with increased apoptosis and reduced branching of the ureteric bud, due to reduced PAX2 dosage during a critical window in kidney development.

To investigate whether PAX2 mutations occur in patients with isolated renal hypoplasia, Nishimoto et al. (2001) analyzed DNA from 20 patients with bilateral renal hypoplasia associated with decreased renal function. Heterozygous PAX2 mutations were detected in 2 patients: 1566C-A (167409.0010) and 1318C-T (167409.0011), respectively. The 2 changes directly introduced stop codons, presumably resulting in a message for a truncated PAX2 protein that lacked a partial transactivation domain. Ophthalmologic examination revealed very mild, asymptomatic coloboma in the second patient, whereas the fundus was normal in the first. The mutation cosegregated with renal hypoplasia in the family of the first patient, appearing de novo in the patient's mother.

In a child with atypical bilateral optic nerve dysplasia and congenital renal hypoplasia, Chung et al. (2001) reported a novel sporadic PAX2 mutation leading to a prematurely truncated protein. The mutation was not found in the parents. The authors concluded that the causal relationship between PAX2 gene mutations and the renal-coloboma syndrome was further supported by this novel mutation.

ALLELIC VARIANTS
(selected examples)

.0001 RENAL-COLOBOMA SYNDROME [PAX2, 1-BP DEL, NT1104]

In a father and 3 of his 5 sons with renal-coloboma syndrome (120330), Sanyanusin et al. (1995) found deletion of nucleotide 1104 in the PAX2 gene (codon 188) causing a frameshift in the coding region that resulted in a stop codon (UGA) 86 codons downstream of the deletion. The frameshift caused truncation of the protein, effectively removing the octapeptide domain and the C-terminal regions of the protein. The mutation appeared to have originated with the father, who was more mildly affected than the sons. The 35-year-old father had bilateral optic nerve colobomas but no renal problems recognized during childhood. An evaluation prompted by the renal problems in his sons demonstrated hypertension, mild proteinuria, and an elevated serum creatinine, but normal renal ultrasound. Ophthalmologic examination showed severe bilateral myopia, scleral staphyloma, and bilateral colobomas. Mild sensorineural hearing loss of unknown cause was also present. The oldest affected son, aged 15 years, had chronic renal failure and severe visual impairment. He first presented at 18 months for investigation of short stature. He already had renal insufficiency and showed a nonfunctioning right kidney and bilateral grade IV vesicoureteral reflux. The last ureteral reimplantation was performed at age 2. Hearing was normal. The second affected son, aged 10 years, had severe visual impairment, optic nerve colobomas, and mild renal dysfunction. He had grade II vesicoureteral reflux and small hypoplastic kidneys with poor corticomedullary differentiation. The third affected son, aged 6 years, had progressive renal failure for which he underwent renal transplantation at the age of 5 years. Schimmenti et al. (1995) reported the clinical features of the affected males in whom the PAX2 mutation was identified by Sanyanusin et al. (1995) (see 120330).

Favor et al. (1996) identified the same mutation in the mouse. Heterozygous mutant mice exhibited defects in the kidney, the optic nerve, and the retinal layer of the eye, while in homozygous mutant embryos, development of the optic nerve, metanephric kidney, and ventral regions of the inner ear was severely affected. In addition, the authors observed deletion of the cerebellum and the posterior mesencephalon in homozygous mutant embryos demonstrating that, in contrast to mutations in PAX5 (167414), which is also expressed early in mid-hindbrain region, loss of PAX2 gene function alone results in the early loss of the mid-hindbrain region. The mid-hindbrain phenotype is similar to Wnt1 (164820) and En1 (131290) mutant phenotypes, suggesting to Favor et al. (1996) the conservation of gene regulatory networks between vertebrates and Drosophila.

.0002 RENAL-COLOBOMA SYNDROME [PAX2, 1-BP INS, 619G]

RENAL HYPOPLASIA, ISOLATED, INCLUDED
In 2 brothers with the renal-coloboma syndrome (120330) reported by Weaver et al. (1988), Sanyanusin et al. (1995) found insertion of a G at position 619 (619insG) of the PAX2 gene (codon 26) resulting in a frameshift and predicted to result in a truncated PAX2 protein due to introduction of a termination codon 26 amino acids downstream from the mutation.

Schimmenti et al. (1997) noted that previously reported patients with renal-coloboma syndrome had ocular and/or renal abnormalities, but PAX2 expression patterns suggested that auditory and CNS abnormalities may be additional features of the condition. To determine whether additional clinical features are associated with PAX2 mutations, they used PCR-SSCP to identify PAX2

gene mutations in patients with a variety of abnormalities. They identified the 619insG mutation in 3 patients from 2 different families. Their patient 657 was a 25-year-old male who was moderately mentally retarded and microcephalic. At age 3 months, he presented with esotropia, exophthalmos, and lack of direct pupillary response to light stimulation of the left eye. The anterior segment of both eyes was normal. The fundi of both eyes were lightly pigmented. In the left eye, no optic nerve head and no retinal vessels were present. In the area where the disc is normally present, a gray structure with an overlying pit was evident. In the right eye, milder changes were observed, including a hypoplastic optic disc with a pit surrounded by pigment, diffuse atrophic changes of the retina, and retinochoroidal colobomas in the inferior fundus. Electroretinography was subnormal in the right eye; responses were electronegative in the left eye. At age 7 years, ultrasound and CT scans showed a retrobulbar cyst behind the left microphthalmic eye. At age 4 months, renal insufficiency was noted with hypoplastic kidneys. The patient's mother, a 48-year-old woman, had hypertension and proteinuria during 2 pregnancies at ages 19 and 22 years. End-stage renal disease and bilateral renal hypoplasia were diagnosed at age 24 years, and she was maintained on hemodialysis waiting for a second renal transplant after failure of her first transplant. Bilateral opacities of the anterior and posterior lens capsules were noted and required surgical treatment. Fundi showed hypoplastic optic discs bilaterally. Visual acuity was 20/30 in both eyes. She had normal intelligence, normal hearing, and no history of seizures. Physical examination was significant for soft skin, which was also noted in her son. The third patient with the 619insG mutation was a 20-year-old female who had developed proteinuria at age 3 years and progressed to end-stage renal disease. Renal biopsy at age 10 years showed focal segmental glomerulosclerosis and renal ultrasound showed small kidneys. Renal transplant from her brother at age 18 years was rejected and the patient was maintained on hemodialysis awaiting a cadaveric transplant. Bilateral optic nerve colobomas were discovered at the age of 6 years. At age 20, she had 'relatively good vision' and did not require corrective lenses. Bilateral inguinal hernias had been repaired at age 6 years.

Tellier et al. (1998) demonstrated that this relatively frequent and recurrent mutation can produce either isolated renal hypoplasia or renal hypoplasia associated with microphthalmia and retinal degeneration. The same mutation is responsible for the Pax2 1Neu mutant, a mouse model for human RCS.

Amiel et al. (2000) described a family in which 3 sibs had renal-coloboma syndrome and the PAX2 619insG mutation. The unaffected parents did not carry the mutation, suggesting the presence of germline mosaicism. The study of a PAX2 intragenic DNA microsatellite marker showed that the mutation was of paternal origin (false paternity was excluded by the study of polymorphic markers).

In a family in which at least 7 members had renal-coloboma syndrome, Ford et al. (2001) identified the 619insG frameshift mutation in all of those affected. The authors noted remarkable variability in both the ocular and renal manifestations.

.0003 RENAL-COLOBOMA SYNDROME [PAX2, 22-BP DEL, NT674]

Schimmenti et al. (1997) demonstrated a deletion of 22 bp at positions 674 to 695, inclusive, in exon 2 of the PAX2 gene in a patient with the renal-coloboma syndrome (120330). The patient was an 11-year-old male who was found at age 3 months to have polyuria, severe proteinuria, and hypertension. Progressive end-stage renal failure developed at 2 years of age, requiring peritoneal dialysis. Renal ultrasound showed bilateral renal hypoplasia. Bilateral retinal and optic nerve colobomas were detected at 3 years of age. His IQ at 9 years was within the normal range. Both

parents were clinically normal and did not carry the mutation.

.0004 RENAL-COLOBOMA SYNDROME [PAX2, 1-BP INS]

In 3 patients with renal-coloboma syndrome (120330), Schimmenti et al. (1997) detected a 1-bp insertion in exon 2 of the PAX2 gene. The insertion of a guanosine residue in exon 2 occurred in a sequence of 7 G's, a sequence which appears to be particularly prone to mutation through slippage during DNA replication.

.0005 RENAL HYPOPLASIA, ISOLATED [PAX2, 6-BP DEL]

Tellier et al. (1998) demonstrated that PAX2 mutations can be responsible for renal hypoplasia, either isolated or associated with various ophthalmologic manifestations ranging from retinal coloboma to microphthalmia. They observed 1 case of isolated renal hypoplasia with a 6-bp deletion of the PAX2 gene.

.0006 RENAL-COLOBOMA SYNDROME [PAX2, GLY75SER]

In a family with renal-coloboma syndrome (120330), Devriendt et al. (1998) identified a heterozygous missense mutation of the PAX2 gene causing a gly75-to-ser (G75S) amino acid substitution. Affected members were thought to have occurred in as many as 5 generations and was well documented in 3 generations.

.0007 RENAL-COLOBOMA SYNDROME [PAX2, 6-BP DUP, NT768]

In a sporadic case of renal-coloboma syndrome (120330) in a male patient with an Oriental mother and Caucasian father, Devriendt et al. (1998) found that the disorder was caused by heterozygosity for a duplication of 6 nucleotides 763-768, i.e., insertion GAGACC after nucleotide 768, resulting in the duplication of amino acid residues glu74 and thr75.

.0008 RENAL-COLOBOMA SYNDROME [PAX2, 1-BP DEL, G, EX2]

In a Caucasian mother and daughter, aged 33 and 5 years, respectively, Schimmenti et al. (1999) identified a 1-bp deletion that resulted in a homoguanine tract from 7 G's to 6 G's in one allele of PAX2. The daughter, the proband, presented to clinic with bilateral optic nerve colobomas and a history of vesicoureteral reflux. Optic nerve colobomas had been discovered during an evaluation for nystagmus and esotropia. She had some limitation of vision. Several urinary tract infections led to the demonstration of vesicoureteral reflux. She had bilateral fourth and fifth digit clinodactyly. The mother had bilateral optic nerve colobomas and a history of urinary tract infections. Renal cysts were identified during childhood by intravenous pyelogram. Diagnosis of bilateral optic nerve colobomas was made incidentally after an eye injury at age 4. Visual acuity was only mildly affected.

.0009 RENAL-COLOBOMA SYNDROME [PAX2, 2-BP INS, 619GG]

In a case of renal-coloboma syndrome (120330), Amiel et al. (2000) reported a dinucleotide insertion GG at position 619 of the PAX2 gene, further confirming the stretch of 7 Gs as a mutation hotspot for spontaneous expansion or contraction mutations. The frameshift mutation was predicted to cause a premature termination of the protein 3 codons downstream from the

mutation.

.0010 RENAL HYPOPLASIA, ISOLATED [PAX2, 1566C-A]

In a patient with bilateral renal hypoplasia and a normal ophthalmologic examination, Nishimoto et al. (2001) found a C-to-A transversion at position 1566 in exon 9 of the PAX2 gene. The nucleotide change directly introduced a stop codon, presumably resulting in a message for a truncated PAX protein that lacked a partial transactivation domain. The mutation cosegregated with the presence of renal hypoplasia in the family, appearing de novo in the patient's mother.

.0011 RENAL HYPOPLASIA, ISOLATED [PAX2, 1318C-T]

In a patient with bilateral renal hypoplasia and very mild asymptomatic coloboma, Nishimoto et al. (2001) found a C-to-T transition at position 1318 in exon 7 of the PAX2 gene. The nucleotide change directly introduced a stop codon, presumably resulting in a message for a truncated PAX protein that lacked a partial transactivation domain. This mutation was not found in the patient's parents or 2 sibs, who exhibited normal kidneys, renal function, and eyes.

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carol : 12/15/1999
mcapotos : 12/15/1999
mcapotos : 12/13/1999
terry : 12/10/1999
kayiaros : 6/21/1999
carol : 11/2/1998
terry : 10/29/1998
dkim : 10/28/1998
carol : 10/26/1998
alopez : 7/30/1997

alopez : 7/7/1997
mark : 6/16/1997
terry : 6/12/1997
alopez : 4/21/1997
alopez : 4/17/1997
alopez : 4/17/1997
terry : 4/11/1997
terry : 1/23/1997
terry : 12/10/1996
terry : 11/12/1996
mark : 9/16/1996
mark : 7/25/1996
mark : 7/23/1996
mark : 1/18/1996
terry : 1/17/1996
mark : 1/16/1996
terry : 1/11/1996
terry : 4/18/1995
carol : 3/8/1994
carol : 4/29/1993
carol : 2/25/1993

ALLELIC VARIANTS
(selected examples)

- 0001 : RENAL-COLOBOMA SYNDROME
  - Mutation : PAX2, 1-BP DEL, NT1104
- 0002 : RENAL-COLOBOMA SYNDROME
  - Mutation : PAX2, 1-BP INS, 619G
- 0003 : RENAL-COLOBOMA SYNDROME
  - Mutation : PAX2, 22-BP DEL, NT674
- 0004 : RENAL-COLOBOMA SYNDROME
  - Mutation : PAX2, 1-BP INS
- 0005 : RENAL HYPOPLASIA, ISOLATED
  - Mutation : PAX2, 6-BP DEL
- 0006 : RENAL-COLOBOMA SYNDROME
  - Mutation : PAX2, GLY75SER
- 0007 : RENAL-COLOBOMA SYNDROME
  - Mutation : PAX2, 6-BP DUP, NT768
- 0008 : RENAL-COLOBOMA SYNDROME
  - Mutation : PAX2, 1-BP DEL, G, EX2
- 0009 : RENAL-COLOBOMA SYNDROME
  - Mutation : PAX2, 2-BP INS, 619GG
- 0010 : RENAL HYPOPLASIA, ISOLATED
  - Mutation : PAX2, 1566C-A
- 0011 : RENAL HYPOPLASIA, ISOLATED
  - Mutation : PAX2, 1318C-T